Docket No.: 20052/1200522-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Randolph J. Noelle et al.

Application No.: 09/835,126 | Confirmation No.: 4674

Filed: April 16, 2001 | Art Unit: 1644

For: *EX VIVO* TREATMENT OF ALLOGENEIC AND XENOGENEIC DONOR T-CELLS CONTAINING COMPOSITIONS (BONE MARROW) USING gp39 ANTAGONISTS AND USE THEREOF | Examiner: P. Gambel

APPEAL BRIEF

Mail Stop: Appeal Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This appellant's Appeal Brief under 37 C.F.R. § 41.37 is submitted in support of their appeal from the Panel Decision from Pre-Appeal Brief Review dated August 3, 2006 in the above-identified patent application.

In accordance with the Pre-Appeal Brief Conference Pilot Program, "[t]he time period for filing an appeal brief will be reset to be one month from mailing of the decision on the request, or the balance of the two-month period running from the receipt of the notice of appeal, whichever is greater." Because the Panel Decision was mailed August 3, 2006, and the Notice of Appeal was filed June 30, 2006, Applicants submit that they are entitled to one month from the mail date of the

Panel Decision to file the present Appeal Brief with no extension fees (i.e., September 3, 2006). Therefore, Appellants submit that this Appeal Brief is timely filed with the payment of a one-month extension of time fee. However, the Commissioner is hereby authorized to charge any unpaid fees deemed required in connection with this Appeal Brief, or to credit any overpayment, to Deposit Account No. 04-0100.

I. Real parties in interest

The real parties in interest are Dartmouth College and the University of Minnesota, the assignees of this application by assignments recorded on October 20, 1998, at Reel 9528, Frame 0027 and at Reel 9527, Frame 0968, respectively.

II. Related appeals and interferences

Related Application Serial Number 09/951,537 is currently under appeal from a Panel Decision from Pre-Appeal Brief Review dated August 3, 2006. The present application, Application Serial Number 09/835,126, filed on April 16, 2001, and PCT application US99/16686, filed on July 29, 1999, claim the benefit of Application Serial Number 09/124,683, filed July 30, 1998, now abandoned.

III. Status of claims[1]

Claims 1-2, 4-7, 10-11 and 13 are pending, rejected and are being appealed. Claims 14-15 have been withdrawn from consideration. Claims 3, 8-9 and 12 have been cancelled.

IV. Status of amendments

The final Office Action was transmitted on December 30, 2005. An Amendment and Response pursuant to 37 C.F.R. 1.116 was submitted to the United States Patent and Trademark Office on February 28, 2006. In an Advisory Action mailed April 27, 2006, the Examiner refused entry of the claim amendments in the Amendment and Response.

On June 30, 2006 a Pre-Appeal Brief Request for Review was submitted in accordance with the Pre-Appeal Brief Conference Program together with a Notice of Appeal. A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on August 3, 2006 wherein the Panel: (1) determined that the application remains under appeal because there is at least one actual issue for appeal; (2) maintained rejection of claims 1-2, 4-7, 10-11 and 13; and (3) noted that claims 14-15 have been withdrawn.

[1] Please note that claims 8 and 9 were cancelled in the Supplemental Amendment filed on September 23, 2005. Page 2 of the final Office Action mailed on December 30, 2005, states that "Applicant's Amendment, filed 9/23/05, has been entered". However, there is a discrepancy between the Examiner's acknowledgment of the Supplemental Amendment canceling claims 8 and 9 and the Examiner's rejection of claims 1, 2, 4-11 and 13 as stated in the remainder of the final Office action. While we address the specific rejections as they appear in the final Office Action, the claims entered in the Supplemental Amendment filed September 23, 2005 are attached hereto in the "Claims Appendix".

V. Summary of claimed subject matter

The present invention provides a successful method for treating donor T-cells *ex vivo* with a gp39 (also known as CD40L or CD154) antagonist and recipient cells to render the donor T-cells substantially non-responsive to recipient antigens (specification, page 1, lines 15-18; page 4, line 14 - page 5, line 3). The invention thus provides a method for preventing or inhibiting Graft Versus Host Disease (GVHD) responses that might otherwise occur upon transplantation of donor tissues into a recipient (specification, Examples 8-10; page 13, line 12 - page 14, line 29; Figures 5A and 5B).

As disclosed and claimed in this application, the inventors have determined that the GVHD response can be controlled by tolerizing donor T-cells *ex vivo* in a specific manner (specification, page 4, line 24 - page 5, line 3). First, $CD4^+$ helper T-cells from the donor are removed and purified. As an additional requirement, recipient alloantigen-bearing cells are irradiated to remove T-cells. Then the purified donor T-cells are incubated with the irradiated recipient cells and a gp39 antagonist in a mixed lymphocyte reaction (MLR) culture (specification, page 7, lines 6-13; page 8, line 22-28). Exposure of the donor $CD4^+$ T-cells to a combination of the gp39 antagonist and irradiated recipient cells causes donor $CD4^+$ T-cells that recognize the recipient cells as foreign to become non-responsive to recipient cell antigens (specification, page 8, lines 6-9). When treated in this manner, transplanted donor tissue does not cause a GVHD reaction in recipients (specification, Examples 8-10; page 13, line 12 - page 14, line 29; Figures 5A and 5B).

VI. Grounds of rejection to be reviewed on appeal

1. Whether claims 1, 2, 4-11 and 13 are unpatentable under 35 U.S.C. § 112, first paragraph, as lacking written description.

2. Whether claims 1, 2, 4-11 and 13 are unpatentable under 35 U.S.C. § 103(a) as obvious over Noelle *et al.* (U.S. Patent No. 5,876,718) (Noelle), in view of Rooney *et al.* (U.S. Patent No. 5,962,318) (Rooney), and in view of Riddell *et al.* (J. Immunol. Methods 128: 189-201) (Riddell) and Sykes *et al.* (U.S. Patent No. 6,006,752) (Sykes), and in further view of Ochoa *et al.* (U.S. Patent No. 5,725,855) (Ochoa) and Knulst *et al.* (Eur. J. Immunol. 23: 299-302, 1993) (Knulst).

VII. Argument

A. Rejection of claims 1, 2, 4-11 and 13 under 35 U.S.C. § 112, first paragraph, as lacking written description

Claims 1, 2, 4-5, 10-11 and 13

The Examiner improperly rejects claim 1, steps (i) and (iii)-(vi), as not supported by a written description of the full scope of the pending claim. Specifically, the Examiner contends that the claim terms "purifying $CD4^+$ T-cells from donor tissue" and "purified donor $CD4^+$ T-cells/T-cell tolerance" in claim 1, steps (i) and (iii)-(vi), respectively, are not supported by the specification (final Office Action, page 2).

With regard to claim 1 and claims 2, 4-5, 10-11 and 13 dependent thereon, the claim terms are clearly supported by the present specification because the present specification provides

numerous examples that explain to those skilled in the art the meaning of the terms "purifying $CD4^+$ T-cells from donor tissue" and "purified donor $CD4^+$ T-cells/T-cell tolerance" as this term is used in steps (iii)-(vi) of claim 1.

Applicants respectfully submit that the term "purifying $CD4^+$ T-cells from donor tissue" in claim 1, step (i), is supported in the specification as filed. The specification specifically discloses that "highly purified $CD4^+$ lymph node T cells" are used as part of the MLR of Example 1 (specification, page 10, lines 26-28). Products from the MLR containing purified $CD4^+$ T cells of Example 1 are then integrated or compared in each of Examples 2-10. Accordingly, all the results obtained and discussed with regard to the ten Examples provided in the specification are based on the use of $CD4^+$ T-cells purified from donor tissue (specification, Examples 1-10, at page 10, line 25 - page 14, line 29).

Further, specific support is found in the specification for claim 1, step (iii), "producing a mixed lymphocyte reaction culture comprising the purified donor $CD4^+$ T-cells and irradiated, T-cell depleted alloantigen-bearing cells obtained from a recipient", in Example 1 at page 10, line 30 - page 11, line 1; page 4, lines 28-30; page 7, lines 7-10; and page 8, lines 6-9 and 22-24.

Specific support is found in the specification for claim 1, step (iv), "adding an anti-gp39 antibody to the culture, thereby initiating a mixed lymphocyte reaction culture comprising purified donor $CD4^+$ T-cells, T-cell depleted recipient alloantigen-bearing cells, and anti-gp39 antibody", in Example 1 at page 10, line 26 - page 11, line 3; page 4, line 30 - page 5, line 1; and Figure 1.

Specific support is found in the specification for claim 1, step (v), "maintaining the mixed lymphocyte reaction culture *ex vivo* for a sufficient time to render the donor $CD4^+$ T-cells substantially tolerant or non-responsive to said alloantigen-bearing cells", in Example 4 at page 12, lines 2-3; page 4, lines 24-27; and page 8, lines 27-29.

Specific support is found in the specification for claim 1, step (vi), "assaying *ex vivo* for induction of donor $CD4^+$ T-cell tolerance or non-responsiveness", at page 9, lines 1-2; page 10, line 26 - page 13, line 10; and Figures 1-4B.

Additionally, claim 1 steps (iii)-(vi), taken collectively, are supported in the specification at page 8, lines 22-29.

As shown above, steps (i) and (iii)-(vi) of claim 1 are fully described and supported by the present specification, and thus, claim 1 and dependent claims 2, 4-5, 10-11 and 13 meet the requirements of written description under 35 U.S.C. § 112, first paragraph.

Claim 6

The Examiner improperly rejects claim 6 as not supported by a written description of the full scope of the pending claim, *i.e.*, that the MLR is maintained "for a time ranging from about 5 to 30 days", and contends that Applicants rely on a generic disclosure regarding time that does not support the claimed species (final Office Action, pages 2 - 3).

Applicants submit that under U.S. law, the term "about" is considered to be "clear, but flexible". *See* MPEP § 2173.05(b)(A) (*citing Ex Parte Eastwood*, 163 U.S.P.Q. 316 (Bd. App.

1968)). Thus, the term "about" does not render claim 6 indefinite, but rather merely adds permissible flexibility to the range provided in the claim. *Id.*

Further, there is no *per se* rule that ranges in claims must correspond exactly with those disclosed in the specification, the "issue is whether one skilled in the art could derive the claimed ranges" from the disclosure provided. *See Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1566 (Fed. Cir. 1991) (citing *Ralston Purina v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Moreover, an applicant "need not be bound to maximum precision for [a claimed range] when the whole tenor of his disclosure indicates approximation." *Eiselstein v. Frank*, 52 F.3d 1035, 1040 (Fed. Cir. 1995).

The specification discloses that "the culture will be maintained for a time sufficient to induce T-cell tolerance" and that "[t]ypically, this time will range from about 1-2 days to 30 days, more typically about 5-15 days, and most typically about 10 days" (specification, page 8, lines 27-29). Further, Example 4 provides that the MLR was maintained for a "ten day cell culture period" (specification, page 12, line 2).

One skilled in the art could readily derive the claimed ranges from the disclosure provided. Also, the claim term "for a time ranging from about 5 to 30 days" is flexible due to inclusion of the word "about." *See Vas-Cath*, 935 F.2d at 1566 (citing *Ralston Purina*, 772 F.2d at 1575); *see* MPEP § 2173.05(b)(A) (citing *Ex Parte Eastwood*, 163 U.S.P.Q. 316). Further, Applicants submit that the "whole tenor of [the specification] indicates approximation" and, thus, that the rejected term is sufficiently supported in the specification as the claimed range falls within the range of cell culture maintenance times described in the specification. *See Eiselstein*, 52 F.3d at 1040.

Claim 7

The Examiner improperly rejects claim 7 as not supported by a written description of the full scope of the pending claim, *i.e.*, that the MLR is maintained "for a time ranging from 6 to 10 days", and contends that Applicants rely on a generic disclosure regarding time that does not support the claimed species (final Office Action, pages 2 - 3).

As noted above in connection with claim 6, there is no *per se* rule that ranges in claims must correspond exactly with those disclosed in the specification, the "issue is whether one skilled in the art could derive the claimed ranges" from the disclosure provided. *See Vas-Cath*, 935 F.2d at 1566 (citing *Ralston Purina*, 772 F.2d at 1575). Further, an applicant "need not be bound to maximum precision for [a claimed range] when the whole tenor of his disclosure indicates approximation." *Eiselstein*, 52 F.3d at 1040.

The specification provides that "the culture will be maintained for a time sufficient to induce T-cell tolerance" and that "[t]ypically, this time will range from about 1-2 days to 30 days, more typically about 5-15 days, and most typically about 10 days" (specification, page 8, lines 27-29). Further, Example 4 provides that the MLR was maintained for a "ten day cell culture period" (specification, page 12, line 2).

Applicants submit that one skilled in the art could derive the claimed ranges "for a time ranging from 6 to 10 days" from the information disclosed in the specification. *See Vas-Cath*, 935 F.2d at 1566 (citing *Ralston Purina*, 772 F.2d at 1575). It is respectfully submitted that the "whole

tenor of [the specification] indicates approximation" and, thus, that the rejected term is sufficiently supported in the specification as the claimed range falls within the range of cell culture maintenance times described in the specification. *See Eiselstein*, 52 F.3d at 1040.

B. Rejection of claims 1, 2, 4-11 and 13 under 35 U.S.C. § 103, as obvious over Noelle, in view of Rooney, and in view of Riddell and Sykes, and in further view of Ochoa and Knulst

Claims 1, 2, 4-11 and 13

The Examiner improperly rejects claims 1, 2, 4-11 and 13 as obvious over a combination of some or all of six references. The Examiner has not established a *prima facie* case of obviousness as set forth by MPEP § 2143 which requires that three basic criteria be met:

(1) the references taken alone or in combination must teach or suggest all the claimed limitations;

(2) there must be some suggestion and/or motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine reference teachings; and

(3) there must be a reasonable expectation of success.

As shown below, the Examiner has failed to establish any one of the basic criteria, let alone all three basic criteria.

The Examiner contends that the claims are obvious over Noelle, in view of Rooney, and in view of Riddell and Sykes "essentially for reasons of record", and in further view of Ochoa and

Knulst, which the Examimer alleges disclose "purification and administrating [sic] purified $CD4^+$ T-cells per se in transplantation regimes" (final Office Action, page 3).

For clarification, given the number of references involved, a summary of the Examiner's rejections and pertinent acknowledgements of record in relation to each of the six references is set forth below:

1. Noelle: The Examiner alleges that Noelle teaches that: (1) $CD4^+$ T-cells are required for the induction of CTL formation; (2) anti-gp39 antibodies may induce allospecific tolerance in both the $CD4^+$ and $CD8^+$ T-cell compartments of the immune system and that this may be a beneficial therapeutic intervention when considering transplant immunology and immunotherapy; (3) the reactivity of anti-gp39 antibodies on T-cells, including $CD4^+$ T-cells; (4) the isolation and *ex vivo* treatment of bone marrow cells; (5) the *in vivo* administration of anti-gp39 antibodies; (6) depleting T-cells from antigen presenting cells; (7) methods to tolerize T-cells *in vitro* with a gp39 antagonist to affect contact dependent helper effector function; that is, to induce T-cell non-responsiveness to desired alloantigens with gp39 antagonists including the use of anti-gp39 antibodies and antigen presenting cells; and (8) various assays to monitor the induction of T-cell tolerance.

The Examiner concedes that Noelle *does not teach*: (1) the purification; and (2) testing of isolated $CD4^+$ T-cells; (3) in a MLR under the claimed conditions. Noelle also does not teach the time ranges recited in claims 6 and 7.

2. Rooney: The Examiner alleges that Rooney teaches: (1) the irradiation of antigen presenting cells to alleviate the activity of other cell types including T-cells given that antigen presentation was still provided; and (2) that effector cells can be helper $CD4^+$ T-cells as well as cytotoxic $CD8^+$ T-cells which can be administered for cellular immunotherapy.

The Examiner concedes that Rooney was provided as *background* to address some basic principles and practices of cell culture and manipulation in the art at the time of invention.

3. Riddell: The Examiner alleges that Riddell teaches cloning and expanding human antigen-specific T-cells, including $CD4^+$ T-cells as well as $CD8^+$ T-cells *ex vivo* over various lengths of time (for up to three months) prior to administration in various therapeutic regimes.

The Examiner concedes that Riddell was not relied upon for teaching adoptive transfer of T-cells to induce an immune response in transplant recipients.

4. Sykes: The Examiner alleges that Sykes teaches monitoring the induction of T-cell non-responsiveness *ex vivo*; that is, that putative immunosuppressive agents can be prescreened by *in vitro* or *in vivo* tests/assays, including those for transplantation by assessing of the ability of a treated T-cell to release a cytokine to determine the effect of an immunosuppressive drug.

5. Ochoa: The Examiner alleges that Ochoa teaches the manipulation of immune cell subsets, including $CD4^+$ T-cells as well as $CD8^+$ T-cells *ex vivo* prior to administration in various therapeutic regimens.

6. Knulst: The Examiner alleges that Knulst teaches the principle role of $CD4^+$ T-cells in GVHD and the advantages of treating or inhibiting said $CD4^+$ T-cells in decreasing morbidity and increasing survival in GVHD patients.

(1) The Examiner has failed to cite references that either alone, or in combination, teach all the limitations of claims 1, 2, 4-11 and 13

The prior art cited by the Examiner does not disclose or suggest certain important features of claims 1, 2, 4-11 and 13. Specifically, steps: (i) "purifying $CD4^+$ T-cells from donor tissue"; and (ii) "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells" as set forth in claim 1 are not taught or suggested by any of the cited references, either considered alone, or in any combination. Further, absent the limitations recited in claim 1 steps (i) and (ii), the specific MLR recited in claim 1 steps (iii)-(v) that is comprised of the cells recited in steps (i) and (ii), is also not rendered obvious.

Noelle, the primary reference relied upon by the Examiner, does not teach (1) that the donor T-cells must be purified $CD4^+$ T-cells, or (2) that the recipient alloantigen-bearing cells or B cells are first irradiated to deplete recipient T-cells (*see* final Office Action, pages 4 and 7). Thus, **Noelle** fails to teach at least two crucial aspects of the invention. **Rooney**, **Riddell**, **Sykes**, **Ochoa**, and/or **Knulst** also do not disclose these limitations and, thus, all the limitations of the claimed invention

are not taught or suggested by the prior art references, either considered alone or in any combination.

a. Claim 1, Step (i): "purifying $CD4^+$ T-cells from donor tissue"

Claim 1 calls for the step of "purifying $CD4^+$ T-cells from donor tissue" (claim 1, step (i)). This claim limitation is not disclosed or suggested by any of the cited references either alone, or in combination, much less in the context of the MLR called for in claim 1. The specification of the application discloses the use of purified $CD4^+$ T-cells from donor tissue and such cells are used in the MLR of Example 1 in the specification (specification, page 10, line 25 - page 11, line 10). The use of purified $CD4^+$ T-cells from donor tissue in Example 1 is important because the products of Example 1 contributed to the results obtained in Examples 2-10 (specification, page 10, line 28; *see also* page 10, line 25 - page 14, line 29; Figures 1-5; and Tables 1-2).

The Examiner concedes that **Noelle** does not teach the purification of $CD4^+$ T-cells for use in a MLR (final Office Action, page 4). Although the Applicants previously argued this point (*see* Amendment, dated June 21, 2005, page 7), the Examiner has never cited a reference disclosing purification of $CD4^+$ T-cells (*see* final Office Action, page 4).

Rooney, Riddell, Sykes, and **Ochoa** are, in fact, silent on the issue of "purifying $CD4^+$ T-cells from donor tissue."

Knulst teaches injections of certain blood fractions to lethally irradiated mice prior to transplant mitigate GVHD (Knulst, Abstract), but does not teach or suggest any *ex vivo*

modification of purified donor cells, much less "purifying $CD4^+$ T-cells from donor tissue" in the context of claim 1, step (i) for use in the MLR of claim 1, step (iii). Thus, Knulst, either alone or in any combination with the other cited references, does not render claims 1, 2, 4-11 and 13 of the claimed invention obvious.

b. Claim 1, Step (ii): "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells"

Claim 1 calls for the "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells" (claim 1, step (ii)). This limitation is not taught or suggested by any of the cited references either considered alone, or in any combination.

The Examiner states that **Noelle** teaches irradiating alloantigen-bearing cells for *ex vivo* stimulation. However, Noelle does not teach or suggest the use of irradiation *to deplete T-cells* from a population of alloantigen-bearing cells. To this end, Noelle merely suggests that T-cells can be depleted by treatment with anti-T-cell antibody--not irradiation (Noelle, col. 10, lines 34-37).

Rooney also does not teach or suggest the use of irradiation to *deplete* recipient T-cells. Opposite to the claimed irradiation of "alloantigen-bearing cells obtained from a recipient to *deplete* recipient T-cells", **Rooney** discloses the general irradiation of alloantigen-bearing cells to *select for* antigen-specific effector cells, including T-cells, the irradiation prevents proliferation of the alloantigen-bearing cells (Rooney, col. 15, lines 2-4, col. 6, lines 17-19) ("Generally, effector cells of the invention comprise cytotoxic T lymphocytes, usually CD8 cells, and helper T lymphocytes, usually CD4 cells"). Thus, Rooney teaches the use of irradiation to deplete alloantigen-bearing cells--not recipient T-cells.

Additionally, **Riddell** and **Sykes** are wholly silent on the use of irradiation to select subpopulations of cells to the exclusion recipient T-cells. However, **Sykes**, like **Noelle**, teaches that anti-T-cell antibodies can lead to T-cell depletion (Sykes, col. 10, ll. 25-27).

Ochoa is directed to methods for *enhancement* of immune response and is silent with regard to the use of irradiation of a population of alloantigen-bearing recipient cells to deplete only $CD4^+$ T-cells. While **Ochoa** mentions that "any method" might be used to deplete immune cells of T cell subsets, **Ochoa** only specifically provides for "the use of magnetic beads" to produce T cell depleted cell populations (Ochoa, col. 14, lines 35-37 and 41-42; *see* Example 1, col. 19, lines 20-39; and Example 3, col. 20, lines 46-48). In Example 1 of **Ochoa**, the immune cell populations are T cell depleted via the use of magnetic beads to about 95% purity (Ochoa, Example 1, col. 19, lines 32-40).

Thus, while **Ochoa** might suggest the use of magnetic beads to create an immune cell population substantially depleted of T cells, it would not have disclosed or suggested to one of ordinary skill in the art the step of "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T- cells" as called for in the present claims for two reasons. Given the unpredictable nature of the art, a disclosure of the use of magnetic beads to create a cell population of depleted T cells would not have led a person of ordinary skill in the art to use irradiation for this purpose. Secondly, and perhaps more important, Ochoa uses magnetic beads to deplete T cells to *enhance* the immune response, a *completely opposite* result from the invention called for in claims 1, 2, 4-11 and 13. Thus, a person of skill in the art would not have relied upon the teachings of

Ochoa, and Ochoa cannot be deemed to teach or suggest this limitation of the method called for in claims 1, 2, 4-11 and 13.

Applicants submit that **Knulst** is wholly silent on the issue of irradiation to select subpopulations of cells. Further, the "lethally irradiated" mice in **Knulst** do not present any alloantigen-bearing cells, let alone the T-cell depleted alloantigen-bearing cells as required in claim 1, step (ii).

Thus, **Noelle**, **Rooney**, **Riddell**, **Ochoa**, **Sykes**, and **Knulst**, when considered alone or in any combination, do not obviate the step of "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells" as recited in claim 1, step (ii), much less use of these irradiated T-cell depleted recipient cells as incorporated in an *ex vivo* MLR in claim 1, steps (iii)-(v).

c. Claim 1, steps (iii)-(v)

Because the limitations of claim 1, step (i), and/or claim 1, step (ii), are not taught or suggested by the prior art, either taken alone or in any combination, the specific MLR comprised of purified $CD4^+$ donor T-cells and irradiated T-cell depleted alloantigen-bearing recipient cells recited in claim 1, steps (iii)-(v), are also not taught or suggested by the cited references. The specific use of purified donor $CD4^+$ T-cells and irradiated T-cell depleted alloantigen-bearing recipient cells is recited directly in claim 1, steps (iii)-(iv), and it is this particular MLR that is maintained in claim 1, step (v), in culture for a sufficient time to render the donor $CD4^+$ T-cells substantially tolerant or non-responsive to the irradiated T-cell depleted alloantigen-bearing recipient cells. Accordingly,

because the two components of the MLR, the purified $CD4^+$ T-cells of step (i) and the irradiated, T-cell depleted alloantigen-bearing cells of step (ii), are not obvious in view of the prior art, the MLR of claim 1 steps (iii)-(v) is also not obvious over the prior art.

(2) The Examiner has failed to cite references or general knowledge that would suggest or motivate one having ordinary skill in the art to modify or combine the reference teachings to arrive at the invention claimed in claims 1, 2, 4-11 and 13

The correct standard for combining prior art references requires that each reference *must provide some suggestion or motivation to combine* those features identified by the Examiner to arrive at the claimed invention (*see* MPEP § 2143). Here the Examiner, states that "[t]here is *no discouragement nor skepticism*" regarding the proposed combination of **Rooney**, **Riddell**, **Sykes**, **Ochoa**, and **Knulst** and, thus, not only makes an incorrect statement, but clearly applies the wrong standard for a finding of obviousness based on the combination of cited prior art (final Office Action, page 7 (emphasis added)).

35 U.S.C. § 103 *requires assessment of the invention as a whole* such that the Examiner must show that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005); *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004); *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1375 (Fed. Cir. 2000). Further, *references must be considered for all that they teach*, and may not be applied out of their own context to render a claimed invention obvious *absent*

any suggestion to do so. Ecolochem, 227 F.3d at 1375. That is, "the 'as a whole' instruction . . . prevents evaluation of the invention part by part." *Ruiz*, 357 F.3d at 1275.

"The suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1998). An Examiner may not use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998) ("Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention."); *Sensonics, Inc. v. Aeronsonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996) ("To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction--an illogical and inappropriate process by which to determine patentability."); *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992) ("The combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a prima facie case of obviousness."); *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (citing *In re Fine,* 837 F.2d 1071, 1075 (Fed. Cir. 1988)); *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991) ("It is impermissible, however, to simply engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps."). That is, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fritch*, 972 F.2d at 1266. Allowing the Examiner to use "the invention as a

roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result--often the very definition of invention." *Ruiz*, 357 F.3d at 1275.

Further, "a reference will *teach away* if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (emphasis added)). That is, a reference which teaches an opposite concept teaches away, and cannot be properly combined to make an obviousness rejection. *In re Lundsford*, 148 U.S.P.Q. 721, 726 (CCPA 1966).

The result achieved by the claimed invention is *induced immunological tolerance*--not *enhanced immunological response*. Thus, upon considering the cited references for all that they teach, one of ordinary skill in the art would not have found any suggestion or motivation to combine any information disclosed in at least **Rooney**, **Riddell**, or **Ochoa**, either considered alone or in combination with the other cited references. As detailed below, **Rooney**, **Riddell**, and **Ochoa** teach enhanced immunological response, an opposite concept from the claimed induced immunological tolerance, and thus teach away from the claimed invention. *Id.*

Rooney seeks to *stimulate* an immune response to specific antigens for adoptive transfer, which is useful to treat infections in immunocompromised individuals, or to treat tumors (Rooney, Abstract) ("The present invention is directed to methods of stimulating primary and secondary effector cell responses for cellular immunotherapy.").

Riddell teaches improved culture methods for "expanding human antigen-specific T-cells" (Riddell, Abstract; *see* final Office Action, page 4).

Ochoa teaches a method "for enhancing the immunotherapeutic activity" of immune cells (Ochoa, Abstract).

The Examiner has in fact already acknowledged that **Riddell** and **Rooney** (like **Ochoa**) may use T-cells to accomplish different endpoints, *i.e.*, enhanced vs. tolerized immune response (final Office Action, page 6). Here, the Examiner has improperly applied these references out of their own context to support an argument that claims 1, 2, 4-11 and 13 are obvious. *See Ecolochem*, 227 F.3d at 1371-72 (emphasis added).

In view of the above, the **Riddell**, **Rooney**, and **Ochoa** references should be removed from consideration in connection with the claimed invention, and the obviousness rejection of the claims 1, 2, 4-11 and 13 should be withdrawn.

(3) The Examiner has failed to cite references that give rise to a reasonable expectation of success of achieving the invention claimed in claims 1, 2, 4-11 and 13

The Examiner has presented references that upon combination with each other and/or with knowledge common to those of ordinary skill in the art at the time of the invention would provide no reasonable expectation of success for achieving the invention claimed in claims 1, 2, 4-11 and 13. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure").

There is no teaching or suggestion in the cited prior art, either considered alone or in any combination, of the features recited in claim 1, step (i), i.e., "purifying $CD4^+$ T-cells from donor tissue", or claim 1, step (ii), i.e., "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells". As noted above in Section VII(B)(1)(c), the specific use of purified donor $CD4^+$ T-cells and irradiated T-cell depleted alloantigen-bearing recipient cells is recited directly in claim 1, steps (iii)-(iv), and it is this particular MLR that is maintained in claim 1, step (v), in culture for a sufficient time to render the donor $CD4^+$ T-cells substantially tolerant or non-responsive to the irradiated T-cell depleted alloantigen-bearing recipient cells. Accordingly, because at least two of the components of the MLR are not obvious in view of the prior art, there would be no reasonable expectation that these components might be used to achieve the MLR of claim 1 steps (iii)-(v).

Further, three of the six references cited by the Examiner teach away from the claimed invention and actually achieve an opposite result to Applicants' claimed invention—*stimulation* of the immune system as opposed to *induced immunological tolerance or non-responsiveness*. Thus, any reliance on these references by one of ordinary skill in the art at the time of the invention would have frustrated their efforts to achieve with any certainty the claimed invention. This is particularly so in view of the fact that modification of the gp39 mechanism to achieve *immunotolerance* is rooted in a highly unpredictable art ((*see* specification, page 2, lines 18-22) (expressing uncertainty and noting that blocking certain T-cell signaling "is *thought* to induce a state of unresponsiveness or anergy in the T-cell, thereby inducing antigen-specific tolerance in the T-cell") (emphasis added); Noelle, col. 1, line 66 - col. 2, line 3 (same)).

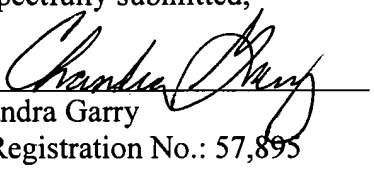
Thus, one of ordinary skill in the art at the time of invention would not have had a reasonable expectation of success based upon any combination of the cited prior art and/or their own knowledge to create the claimed methods of using an MLR comprising purified donor $CD4^+$ T-cells, irradiated, T-cell depleted recipient alloantigen-bearing cells, and a gp39 antagonist to induce immunotolerance or non-responsiveness in the donor $CD4^+$ cells.

VIII. Conclusion

For the foregoing reasons the Examiner's rejections of the pending claims should be reversed.

Dated: October 3, 2006

Respectfully submitted,

By 

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CLAIMS APPENDIX

1. (Rejected) A method for inducing T-cell tolerance or non-responsiveness of donor T-cells to desired alloantigen-bearing cells *ex vivo* comprising the following:

(i) purifying $CD4^+$ T-cells from donor tissue;

(ii) irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells;

(iii) producing a mixed lymphocyte reaction culture comprising the purified donor $CD4^+$ T-cells and irradiated, T-cell depleted alloantigen-bearing cells obtained from a recipient;

(iv) adding an anti-gp39 antibody to the culture, thereby initiating a mixed lymphocyte reaction culture comprising purified donor $CD4^+$ T-cells, T-cell depleted recipient alloantigen-bearing cells, and anti-gp39 antibody;

(v) maintaining the mixed lymphocyte reaction culture *ex vivo* for a sufficient time to render the donor $CD4^+$ T-cells substantially tolerant or non-responsive to said alloantigen-bearing cells; and

(vi) assaying *ex vivo* for induction of donor $CD4^+$ T-cell tolerance or non-responsiveness.

2. (Rejected) The method of Claim 1, wherein the donor tissue is donor bone marrow or peripheral blood cells.

3. (Canceled)

4. (Rejected) The method of Claim 1, wherein the gp39 antibody is an anti-human gp39 monoclonal antibody.

5. (Rejected) The method of Claim 4, wherein said anti-gp39 antibody is a chimeric or humanized anti-human gp39 monoclonal antibody.

6. (Rejected) The method of Claim 1, wherein the donor T-cells are cultured in step (v) for a time ranging from about 5 to 30 days.

7. (Rejected) The method of Claim 6, wherein said donor T-cells are cultured in step (v) for a time ranging from 6 to 10 days.

8-9. (Canceled)

10. (Rejected) The method of Claim 1, wherein the donor T-cells that have been determined to be tolerized by the assay of step (vi) are transplanted into a recipient in need of such transplantation.

11. (Rejected) The method of Claim 10, wherein the recipient is in need of immune reconstitution as a result of disease or disease treatment.

12. (Canceled)

13. (Rejected) The method of Claim 1, wherein the step of assaying for induction of donor T-cell tolerance or non-responsiveness comprises measuring IL-2 concentration in the cell

culture medium supernatants of the donor T-cells cultured in step (v) and of control donor T-cells, wherein detection of reduced IL-2 concentration in the supernatant of the donor T-cells cultured in step (v), relative to the IL-2 concentration in the supernatant of control T-cells, is indicative of substantial donor T-cell tolerance or non-responsiveness to the alloantigen-bearing cells.

14. (Withdrawn) The method of Claim 1, wherein the step of assaying for induction of donor T-cell tolerance or non-responsiveness comprises measuring the concentration of interferon-gamma in the cell culture medium supernatants of the donor T-cells cultured in step iv and of control donor T-cells,

wherein detection of reduced interferon-gamma concentration in the supernatant of the donor T-cells cultured in step iv relative to that of the control T-cells is indicative of substantial donor T-cell tolerance or non-responsiveness to the alloantigen-bearing cells.

15. (Withdrawn) The method of Claim 1, wherein the step of assaying for induction of donor T-cell tolerance or non-responsiveness comprises assaying to detect at least one antigen selected from the group consisting of L-selectin, ICAM-1, and CD45 in the donor T-cells cultured in step iv and control donor T-cells,

wherein detection of an increased amount of L-selectin or ICAM-1, or a reduced amount of CD45 in the donor T-cells cultured in step iv relative to that in the control donor T-cells is indicative of substantial donor T-cell tolerance or non-responsiveness to the alloantigen-bearing cells.

EVIDENCE APPENDIX

None

RELATED PROCEEDING APPENDIX

(1) Panel Decision from Pre-Appeal Brief Review dated August 3, 2006.

(2) Panel Decision from Pre-Appeal Brief Review dated August 3, 2006 for related Patent Application Serial Number 09/951,537.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,126	04/16/2001	Randolph J. Noelle	20052/1200522-US1	4674

7278 7590 08/03/2006

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	09/835,126	NOELLE ET AL.	
	Phillip Gambel	Art Unit 1644	
Document Code - AP.PRE.DEC			

Notice of Panel Decision from Pre-Appeal Brief Review

This is in response to the Pre-Appeal Brief Request for Review filed 6/30/06.

1. ☐ **Improper Request** – The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☒ **Proceed to Board of Patent Appeals and Interferences** – A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☒ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: *none*.
Claim(s) objected to: *none*.
Claim(s) rejected: *1-2, 4-7, 10-11 and 13*.
Claim(s) withdrawn from consideration: *14-15*.

3. ☐ **Allowable application** – A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☐ **Reopen Prosecution** – A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) *Phillip Gambel*.

(2) *Larry Helms, SPE 1643*.

(3) *Christina Chan, SPE, 1644*. Christina Chan

(4)____.

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GAMBEL, PHILLIP	

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